THE MEDICAL LETTER

a non-profit publication

on Drugs and Therapeutics

Published by Drug and Therapeutic Information, Inc., 136 East 57th Street, New York 22, New York

Vol. 1, No. 8 May 1, 1959

DEAFNESS CAUSED BY ANTIBIOTICS

The fact that injections of dihydrostreptomycin can cause irreversible deafness has been known for many years, and has been the subject of a number of cautionary reports (see "Current Concepts of Therapy" – N. E. J. Med., 259:85, 538, 1958). The drug continues to be widely used, nevertheless, largely in the belief that hearing damage results only from large or prolonged dosage.

A report on "Dihydrostreptomycin Deafness" by Dr. George E. Shambaugh, Jr. and seven other otolaryngologists, which is soon to be published, questions whether the drug can be safely used in any dosage. Dr. Shambaugh is Professor of Otolaryngology at the Northwestern University School of Medicine.

Over a four-year period, Dr. Shambaugh and his colleagues observed 22 cases of irreversible loss of hearing directly attributable to dihydrostreptomycin and additional cases probably caused by the drug. In some of the cases deafness resulted from injections given "not for severe infections as life-saving measures, but prophylactically in uninfected surgery cases or for mild, common infections ...." In nine of the cases reported, the total dosage of the drug was between one and five grams.

It has been known for some time that the loss of hearing with dihydrostreptomycin is often progressive after use of the drug is stopped. Furthermore, there can be a latent period of several weeks to as long as six months between the administration of the drug and the onset of hearing loss. Because of this latent period, the report says, "The prescribing physician usually had not the remotest idea of the eventual disastrous results."

INCIDENCE OF HEARING LOSS - The authors refer to the paper by A. Glorig (Annals of Otology, Rhinology and Laryngology, 60:327, 1951) which reported loss of hearing in about a third of a group of tuberculosis patients who had received dihydrostreptomycin in doses of two to seven grams weekly for several weeks. Dr. Shambaugh and his colleagues recommend that "...this antibiotic should be omitted from commercial combinations of antibiotics or, if included, its presence should be clearly indicated in the name. Since streptomycin is as effective as dihydrostreptomycin for gram-negative and acid fast [bacillary] infections and since toxic reactions occur immediately, are more easily recognized, and less permanently disabling, there seems to be little reason to utilize the more dangerous drug." (Streptomycin can cause irreversible

vestibular damage, affecting balance, but patients can learn to compensate for this impairment.) If dihydrostreptomycin is absolutely essential, as for treatment of seriously ill tuberculosis patients who are sensitive to streptomycin, as small a dose for as short a period as possible should be used.

The report lists the following mixtures of dihydrostreptomycin with other antibiotics among the agents responsible for deafness in the series observed: Dicrysticin (Squibb), Dihydrocillin (Upjohn), S-R-D (Parke-Davis), Distrycillin (Squibb), Bicillimycin (Wyeth), Cillimycin (Wyeth), Combiotic (Pfizer), Durycin (Lilly), Crysdimycin (Squibb), and Strocillin (Abbott).

KANAMYCIN AND NEOMYCIN DEAFNESS - Dihydrostreptomycin is not, of course, the only antibiotic that can affect hearing. The Medical Letter cautioned, in its "pre-publication" issue, that irreversible loss of hearing may follow the parenteral use of kanamycin (Kantrex-Bristol), and that this drug should be used parenterally only for severe staphylococcus or other infections, and only after safer antibiotics had proved ineffective. In view of the current promotion of Kantrex as "the logical 'first-choice' antibiotic," the following statement by Dr. Shambaugh and his colleagues is significant: "Because of its known ototoxicity, neomycin is now restricted to non-parenteral use except as a life-saving measure. Kanamycin may soon be relegated to a similar category" (our emphasis).

BUTAZOLIDIN AND STERAZOLIDIN

Phenylbutazone (Butazolidin - Geigy) has the unhappy distinction of causing a higher incidence of toxic and side effects than almost any other widely used drug. These effects, variously reported as occurring in from 25% to 60% of patients, are usually mild, but in a considerable percentage of patients they are severe, and they can be fatal. Butazolidin is effective in many inflammatory conditions, but safer drugs are available for the treatment of almost all of these conditions. Butazolidin should be used only where the benefits outweigh the risks.

Although colchicine is the drug of choice in acute gout, Butazolidin can be used alone or as an adjunct to colchicine. Where full doses of colchicine cannot be tolerated, smaller doses may be prescribed along with 800 mg. of Butazolidin during the initial 12 hours (J. H. Talbot, Disease-a-Month series, Year Book Publishers, March, 1957). Some clinicians use Butazolidin for long-range therapy of severe rheumatoid spondylitis; despite its toxic effects they consider it far safer than radiotherapy of the spine.

RHEUMATOID ARTHRITIS - While Butazolidin is sometimes helpful in rheumatoid arthritis, osteoarthritis, and the non-articular rheumatisms such as bursitis and painful-shoulder syndrome, results are not predictable, and toxic reactions are frequent. Bursitis and painful-shoulder syndrome can often be treated effectively with aspirin along with cold or iced compresses for the acute phase followed by heat and physiotherapy.

Butazolidin is also recommended by the manufacturer for the treatment of acute superificial thrombophlebitis. In a review of this disorder (S. Wessler

and D. Deykin, Circulation, 18:1202, 1958), the authors point out that the symptoms of acute thrombophlebitis usually "are not severe and subside spontaneously following a few days of bed rest and leg elevation." Because of the hazards associated with the use of Butazolidin, the authors state that they have avoided this drug "...despite the currently favorable claims in the literature."

TOXIC REACTIONS - Severe toxic reactions requiring discontinuance of the drug have occurred in as many as 18% of patients in some series of cases. According to the 12th Rheumatism Review of the Amer. Rheumatism Assn. (Annals of Internal Medicine, 50:366, 1959), "The most frequent reactions were gastrointestinal disturbances (30% [of reactions]), fluid retention (19%), dermatitis (14%), hematologic disturbances (11%), and exacerbation or bleeding of peptic ulcers (3%)." Large doses of Butazolidin may stimulate excessive adrenal steroid secretion.

Up to 1955, 23 deaths attributed to Butazolidin were reported, most of them from agranulocytosis and other hematologic complications. Butazolidin is contraindicated in the presence of peptic ulcer (or a history of peptic ulcer), cardiac, hepatic or renal disease, erythematous eruptions, and a history of drug allergy or blood dyscrasia. The use of the drug by elderly patients is also considered inadvisable.

Opinions differ as to whether the incidence of adverse effects is related to dosage, but it is probable that the incidence increases with size of dose and duration of treatment. Even in short-term therapy of a week or so, however, undesirable side effects occurred in 9% of a large series of patients.

PRECAUTIONS - Because of the possibility of severe and even fatal reactions, when Butazolidin therapy is prolonged for more than a week, the patient should be examined weekly during the first month, and then every two or three weeks as long as Butazolidin is continued. Repeated examinations of blood, urine and stool have been recommended to detect reactions, but negative results may give a false sense of security. The patient should be alerted to report fever or sore throat (which may be symptoms of agranulocytosis) and any gastrointestinal symptoms, eruptions, edema, or bleeding.

Butazolidin Alka capsules, which contain aluminum hydroxide, magnesium trisilicate, and homatropine methylbromide in addition to Butazolidin, are supposed to reduce gastrointestinal side reactions; their effectiveness for such purpose remains to be established.

Sterazolidin is offered by Geigy as a combination of prednisone (1.25 mg.) and phenylbutazone (50 mg.) together with antacids and homatropine. The combination has the disadvantage not only of an inflexible ratio between two drugs, but also of the double hazard of two very potent drugs each with a high incidence of side reactions in the recommended dosage.

The Geigy Company is known to be searching for methods of altering Butazolidin which will retain or enhance the beneficial properties of the drug while diminishing its toxicity.

FUNGIZONE

Three years of clinical evaluation have shown that amphotericin B (Fungizone-Squibb), derived from a strain of Streptomyces, is the most promising drug now available for the treatment of systemic fungous disease, particularly coccidioidomycosis, histoplasmosis, cryptococcosis (torulosis), systemic moniliasis, and North and South American blastomycosis (M. L. Littman, et al., Am. J. of Med., 24:568, 1958; V. D. Newcomer, et al., J. of Chronic Diseases, 9:353, 1959).

This drug has particular importance for southwestern United States, where soil dust carrying the mold Coccidioides immitis has infected hundreds of thousands of persons and caused many deaths; and for the midwestern and southern states, where another soil organism, Histoplasma capsulatum, has caused equally widespread infection. Most infections with these organisms are mild and subside spontaneously; often they are not detected. But until the introduction of Fungizone, there was no means of treating the severe, systemic infections.

INTRAVENOUS ADMINISTRATION - Fungizone given orally is absorbed only to a very slight degree and does not yield appreciable blood levels. Despite a few reports indicating therapeutic effectiveness of oral administration, it is generally accepted that systemic fungous disease can be cured only when the drug is given intravenously, a procedure requiring hospitalization of the patient. The following details of administration are based on more recent information than that contained in the manufacturer's package leaflet: Fungizone is administered by infusion over a six-hour period every other day for from two to four months. The initial adult dose is 0.4 mg. per kilogram of body weight, increasing in subsequent infusions by increments of 0.2 mg. per kg. to reach a full adult dose of 1 to 1.5 mg. per kg., as tolerated by the patient. Each daily dose is dissolved in 500 cc. of distilled water containing 25 gm. of glucose (to which may be added 2 to 4 mg. of heparin as prophylaxis against thrombophlebitis). The solution is administered at the rate of about 20 drops per minute.

Too high dosage may cause azotemia, which subsides on reduction of the dosage. Too rapid infusion depresses cardiac conduction. Neither of these effects is likely to occur if the recommended dosages are not exceeded. While there have been no reports of permanent adverse effects on the heart, liver, bone marrow, central nervous system or skin, experience with the drug is still limited. A Medical Letter consultant cautions that renal injury may occur late in the course of therapy. Patients on prolonged therapy should have frequent liver, kidney and blood studies. There are fairly frequent, mild side effects, such as nausea, flushing, chilliness, fever and generalized pain, which may disappear as treatment continues.

OTHER USES - Depending on the nature of the infection, Fungizone can also be administered intrathecally, intra-articularly, intrathoracically, and by aerosol inhalation. (For details, see Littman, cited above.) It can be used on the conjunctiva and injected into the anterior chamber of the eye. (For details, see J. B. T. Foster, et al., AMA Arch. of Ophth., 60:555, 1958). It may also be effective by subcutaneous injection in chromoblastomycosis of the skin and subcutaneous tissue (see M. J. Costello, et al., AMA Arch. of Derm., 79:184, 1959).

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS is published fortnightly by Drug and Therapeutic Information, a non-profit corporation, 136 E. 57th St., New York 22. N. Y. Second-class postage paid at New York, N. Y. The subscription fee is $12.50 per year ($6.25 for residents, internes and students).